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Use of Levosimendan in Intensive Care Unit Settings: An Opinion Paper

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Abstract

Levosimendan is an inodilator that promotes cardiac contractility primarily via calcium sensitization of cardiac troponin C and vasodilatation via opening of adenosine triphosphate-sensitive potassium (K_{ATP}) channels in vascular smooth muscle cells; the drug also exerts organ-protective effects via a similar effect on mitochondrial K_{ATP} channels.

This pharmacological profile identifies levosimendan as a drug that may have applications in a wide range of critical illness situations encountered in intensive care unit medicine: hemodynamic support in cardiogenic or septic shock; weaning from mechanical ventilation or from extracorporeal membrane oxygenation; and in the context of cardiorenal syndrome.

This review, authored by experts from 9 European countries (Austria, Belgium, Czech republic, Finland, France, Germany, Italy, Sweden, and Switzerland) examines the clinical and experimental data for levosimendan in these situations and concludes that, in most instances, the evidence is ~~affirmative and~~ encouraging, which is not the case with other cardio- and vasoactive drugs routinely used in the intensive care unit. The size of the available studies is, however, limited and the data are in need of verification in larger controlled trials. Some proposals are offered for the aims and designs of these additional studies.

Key words: inodilator; hemodynamic support; cardiogenic shock; septic shock; weaning; mechanical ventilation; extracorporeal membrane oxygenation; cardiorenal syndrome

1. The calcium sensitizer levosimendan

Levosimendan is a positive inotropic compound with vasodilatory properties [1] used for the treatment of acute decompensated heart failure (HF), and in cases where the use of an inotropic treatment is considered appropriate [2]. The principal mechanism of levosimendan is the sensitization of troponin C to calcium in cardiac muscle [3–5], which leads to its unique feature of exerting a positive inotropic effect without increasing myocardial oxygen consumption [6–10]. In addition, levosimendan opens adenosine triphosphate-sensitive potassium (K_{ATP}) channels in vascular smooth muscle cells [11,12] and induces vasodilation of the pulmonary [13], coronary [14,15] and peripheral arteries [16] and of the venous circulation [17] . By addressing both cardiac inotropy and vascular dilatation, levosimendan improves cardiovascular coupling and cardiac mechanical efficiency. Levosimendan also opens mitochondrial K_{ATP} channels [18] and exerts an organ- and, especially, cardioprotective effect in various settings [19,20]. At higher doses, the drug also acts as a phosphodiesterase type 3 (PDE3) inhibitor [1,12,21,22]. The effects of levosimendan are not impaired by the concomitant use of beta-blockers [23].

Levosimendan has been studied in several therapeutic applications, particularly in the management of acute HF (AHF) patients with low cardiac output [24,25] and in high-risk cardiac surgery [26,27]. Levosimendan has also shown preliminary positive effects in a range of other

conditions requiring inotropic support, including right ventricular failure, cardiogenic shock (CS), septic shock and Takotsubo cardiomyopathy [28].

Owing to its pharmacology, it has become apparent that levosimendan may also have applications in the setting of intensive care medicine. The conceptual framework for this wider use of levosimendan has been set out by Farmakis et al. [28] and is supported by an array of experimental and observational research [29–37] (see **Box 1**).

This commentary identifies a range of clinical situations encountered in the intensive care unit (ICU) where levosimendan may offer clinical advantages, either as an adjunct to standard-of-care therapies or as an alternative to conventional therapies (see **Box 2**).

2. Hemodynamic support in cardiac critical care

In severe AHF and CS, congestion and hypoperfusion lead to a systemic disorder that potentially affects all vital organs. Restoring adequate cardiac output and organ perfusion, and promoting decongestion, are therefore medical priorities during the early phase of treatment [38–40].

In AHF leading to tissue hypoperfusion, initial use of an inotrope is advocated [40,41]. Hence, inotropic support remains a cornerstone of AHF management in these critically ill patients, together with adequate fluid resuscitation (or depletion) and optimization of arterial pressure to suit the individual features of patients.

Reported rates of inotropic support in AHF management vary from 9% in an early US registry [42] to >30% in a later international registry [43] and 13% in the 2017 European Society of Cardiology (ESC) Heart Failure Long-Term Registry [44]. Robust secular trends in the use of inotropes are hard to identify from these fluctuations but dobutamine remains the most frequently used inotrope.

The indication for inotropic support depends largely on the etiology; heading this hierarchy is CS, for which, by definition, virtually all patients are supported by at least one inotropic drug [45]. In septic shock, inotropic support is deployed according to current precepts of early goal-directed therapy (EGDT); in recent EGDT trials, rates of inotrope use ranged from ≈15% for patients included in the intervention groups to usually <5% for those in the standard-of-care groups [46]. The prevalence of inotropic support at admission was 15–20% in a recent pragmatic multicenter trial of levosimendan in septic shock [37]. Inotropic support may also be considered in cases of obstructive shock, whilst waiting for the obstruction to be removed, but continuation after that point would be uncommon.

Dobutamine is the first-line inotropic agent for resuscitating patients suffering from either severe AHF and low cardiac output syndrome [40] in CS [41,47] or septic shock [48] but its administration entails substantial addition of exogenous catecholamines to the endogenous ones already overproduced by the intense activation of the sympathetic autonomous nervous system.

The resulting exacerbation of the beta-adrenergic pathway induces an increase in myocardial oxygen consumption via chronotropic and inotropic effects [49]. This catecholamine-induced myocardial oxygenation imbalance exacerbates myocardial ischemia [50,51], especially at the

level of the subendocardium [52]. Inter alia, excessive adrenergic stimulation is also established as a key factor in the pathophysiology of Takotsubo cardiomyopathy [53] and contributes substantially to some manifestations of the septic cardiomyopathies [54].

Various large international registries relating to AHF and CS have documented higher rates of morbidity and mortality in patients treated with adrenergic inotropes than in severity-matched peers who did not receive catecholamines [42–45]; a recent meta-analysis of randomized clinical trials of dobutamine to treat severe (acute or chronic) HF likewise indicated an increased risk of mortality [55]. These observations, with others [56], are the basis of the European Society of Intensive Care Medicine AHF/CS guidance that "The use of these [inotropic/vasopressor] agents should, however, be restricted to the shortest possible duration and lowest possible dose to maintain perfusion pressure" [57] and the declaration in the ESC HF guidelines that "There is long-standing concern that [inotropes, especially those with adrenergic mechanisms] may increase mortality" [40].

In a randomized clinical trial involving patients with acutely exacerbated chronic HF, the PDE3 inhibitor milrinone was shown to increase mortality in patients suffering from ischemic cardiomyopathy [58]: a similar finding was also reported in a recent large retrospective cohort study of intraoperative inotropic support in cardiac surgery [59]. These data indicate that milrinone (and, by extension, other PDE3 inhibitors) is not a fully satisfactory alternative to dobutamine. Similar reservations apply to dopamine [44,60] and epinephrine [45,61].

The ‘decatecholaminization’ of the critically ill patient represents a new and still-evolving paradigm in the treatment of patients in the ICU [62,63]. One avenue for research in this area has been the evaluation of non-adrenergic vasoactive agents [64–66]. These include levosimendan, which offers positive cardiovascular effects (ventriculo-arterial recoupling, decongestion and cardiac protection against ischemia–reperfusion injury) as well as potentially advantageous ancillary effects on kidney function and diaphragm muscular fibers, as discussed later in this review.

3. Levosimendan in cardiogenic shock

Acute myocardial infarction (AMI) is the most common etiology of CS but CS may arise from any situation of acute, severe dysfunction in either ventricle of the heart. CS is relatively rare but often fatal [67].

The standard of care in CS consists of primary percutaneous coronary intervention (PCI) for AMI, fluid therapy, vasopressors, inotropes and, in the last resort, mechanical assistance [68]. Data from initial comparator studies indicate that levosimendan may be a useful addition to this regimen.

Levosimendan may be a constructive alternative to conventional inotropes for the management of CS. In a trial of 22 consecutive AMI patients who developed CS after PCI, levosimendan (24 µg/kg bolus, then 0.1 µg/kg/min for 24 h) attained the study endpoint of ≥30% increase in cardiac power output (CPO) consistently better than dobutamine (initial dose 5 µg/kg/min, with subsequent dose increases to reach the desired hemodynamic effect) despite a comparable reduction in pulmonary capillary wedge pressure [69] (**Figure 1**). (CPO is the product of cardiac

output and mean arterial pressure [MAP] and an indicator of cardiac contractility and ventricular–vascular coupling: in effect, it represents the pumping power of the heart and has been identified as the strongest predictor of survival in patients with CS [70].)

Levosimendan also compared favorably with the PDE inhibitor enoximone in an exploratory open-label study of CS secondary to AMI, giving a small but significant advantage in death from multi-organ failure ($p \approx 0.02$) [71]. Beneficial hemodynamic effects were recorded in both groups, including enhancement of CPO, but these changes were achieved sooner with levosimendan than enoximone. There was a significant advantage with levosimendan in terms of fewer deaths from multi-organ failure ($p < 0.05$). Use of dobutamine and norepinephrine in the levosimendan-treated patients was much lower than that in the enoximone group. It is plausible that part of the survival advantage seen with levosimendan may be attributable to a reduction in exposure to exogenous catecholamines.

Notwithstanding these data, levosimendan is currently regarded as a salvage therapy in CS after dobutamine failure and before extracorporeal life support (ECLS). Any revision of this status will require well-designed randomized controlled studies [72]. Until then, the use of levosimendan may be considered in cases of low cardiac output associated with signs of hypoperfusion or deteriorating renal/liver function, especially if beta-blocker use is part of the clinical scenario.

Use of levosimendan is contraindicated in hypovolemia, which must be excluded using echocardiography and/or advanced monitoring and dynamic indices. Cardiac output monitoring (transpulmonary thermodilution or pulmonary artery catheterization in cases of associated right ventricular dysfunction) is highly recommended.

Omitting a loading dose seems a rationale choice, while the maintenance infusion for a total duration of 24 h (0.05-0.2 mcg/kg/min) should be individually adjusted. After levosimendan is started, dobutamine may be weaned according to the hemodynamic and clinical response (generally after 2 h). As soon as possible, but after weaning of vasopressors, established chronic HF treatments should be (re-)introduced.

In practice, systolic and diastolic dysfunction often coexist. The management of circulatory failure related to diastolic dysfunction in critical illness is largely supportive. Adequate fluid resuscitation is often followed by the administration of drugs with a positive lusitropic effect. Levosimendan has been shown to improve diastolic function [73] and filling and, importantly, it can be safely combined with beta-blockers, which represent one of the potential treatment modalities for diastolic dysfunction.

4. Levosimendan in septic shock

Sepsis is defined nowadays as an infection inducing dysfunction of at least one organ owing to a deregulated host inflammatory response [74]. In addition to intrinsic distributive shock due to vascular hyporeactivity and autonomic dysfunction, sepsis can also induce septic cardiomyopathy (SCM) with de novo AHF due to myocardial depression. Such complications

contribute to a sepsis mortality rate of ≈30% [74,75]. The prevalence of SCM among septic patients varies widely (from 20–60%), a state of affairs that reflects both the current lack of a common definition and the heterogeneity of the symptoms [75].

Inotropic support is endorsed for restoration of an adequate cardiac output and peripheral oxygen delivery [48]. In the absence of a fully evidence-based alternative, dobutamine remains the suggested first-line inotrope for those goals, despite observations that: (1) high levels of circulating catecholamines and adrenergic overstimulation contribute to the pathophysiology of SCM [54,76]; (2) the adrenergic response at the cardiomyocyte level is attenuated by downregulation of β-adrenergic receptors [77,78]; (3) adrenergic drugs have been associated with worse outcomes in a pooled network meta-analysis [36]; and (4) esmolol, a β_1-receptor antagonist, seems to improve the outcome of severe SCM [78], especially in cases of persistent tachycardia [79].

Proceeding from the above points, assessment of levosimendan as an alternative inotropic drug in septic shock should address the following clinical goals and criteria.

1. Dobutamine-sparing: reducing the high (toxic) levels of endogenous and pharmacological adrenergic stimulation and hence restoring a better myocardial oxygenation balance, particularly in the case of coronary artery disease (CAD) with potential catecholamine-induced ischemia [51].
2. Attenuation of multiple-organ failure (MOF): reducing the occurrence and/or severity of sepsis-induced MOF due to better regional blood flow distribution in addition to a global

increase in cardiac output, plus pleiotropic effects at the cellular and mitochondrial levels [28,80].

3. Inotropic rescue therapy: restoring inotropic responsiveness in cases of severely attenuated adrenergic response.
4. Drug safety: replacing adrenergic inotropic drugs without tachyarrhythmia or any additional requirement for vasopressors.

Experimental studies (mainly in animal models of peritonitis-induced septic shock) have demonstrated an improvement in survival, a reduction in the severity of MOF and anti-inflammatory protective effects with levosimendan [80,81]. It must be acknowledged, however, that many of those studies were restricted to comparison versus placebo, not other inotropes.

As regards clinical trials of levosimendan in septic shock, in a monocentric randomized controlled trial, a 24-h infusion of levosimendan (0.2 µg/kg/min) was compared with dobutamine (5 µg/kg/min) as inotropic support for patients with de novo severe SCM (n=28) and a left ventricular ejection fraction (LVEF) <45% despite 48 h of conventional standard-of-care treatment, including dobutamine [82]. Levosimendan use was associated with increases in cardiac output and pulmonary decongestion, without an increase in vasopressor requirements (owing to volume expansion), and with more favorable evolution of various MOF surrogates (lactate clearance, veno-arterial carbon dioxide gap, gut mucosal perfusion and renal function). Dobutamine did not materially alter any of these systemic or regional hemodynamic variables.

The findings of this study satisfy the clinical goals identified above and are, to that extent, promising regarding the potential of levosimendan in sepsis and SCM. However, this was a single study with several limitations and must be considered indicative, not definitive [83].

The biological mechanisms underpinning this attenuation of MOF have been explored in subsequent clinical trials: levosimendan infusion has been shown to improve microcirculation perfusion [84], relieve mitochondrial oxidative stress [85] and restore the muscular lactate/pyruvate ratio [86]. Some of this research, plus additional small clinical trials of heterogeneous quality, has been incorporated into a meta-analysis [87] of the effects of levosimendan in septic shock versus standard inotropes (invariably dobutamine where specified). Findings from this exercise (seven studies, 249 patients) included a significant reduction in mortality in the levosimendan group without intergroup differences in MAP or norepinephrine usage.

These clinical observations, together with a strong experimental background, led to the development of a large pragmatic multicenter randomized placebo-controlled trial of levosimendan in sepsis. This study – Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS; ISRCTN12776039) – examined whether early administration of levosimendan (0.05–0.2 μg/kg/min for 24 h) could avert the onset of MOF in a broad population of septic shock patients (n=516) fulfilling the criteria for systemic inflammatory response syndrome due to infection, and requiring vasopressor therapy for at least 4 h [37].

LeoPARDS did not fulfill the primary endpoint of a significant intergroup difference in mean daily Sequential Organ Failure Assessment score favoring levosimendan, and nor was mortality reduced. While prima facie disappointing, these findings should be considered in perspective. This was a relatively low-risk cohort; most patients were not suffering from either severe circulatory shock or severe SCM needing inotropic support. Moreover, the degree of renal replacement therapy already being undertaken before randomization was substantial and may have led to faster elimination of the study drug in 17% of patients in the intervention group. These reasons may have resulted in LeoPARDS lacking the necessary focus to identify an effect of levosimendan on the patients who could have benefitted. ~~From a safety perspective, however, levosimendan infusion was broadly very well tolerated.~~

The currently available clinical evidence in septic shock indicates that: (a) Levosimendan can successfully replace dobutamine in supporting severe de novo AHF due to SCM, with additional positive extra-cardiac effects owing to amelioration of MOF. These results need to be replicated on a larger scale; and (b) Indiscriminate use of levosimendan (i.e. without selecting severe cases of cardiovascular failure) to prevent the development of MOF is safe from a hemodynamic perspective but may confer no clinical benefit.

In addition, however, recent data from patients in septic shock show ventriculo-arterial uncoupling due to either ventricular elastance reduction (as in SCM) or increased arterial elastance due to vasopressor therapy, or both: this is a situation in which cardiac mitochondrial function can be severely impaired and the oxygen metabolism altered [88]. No data are currently published on the effect of levosimendan on ventriculo-arterial coupling in septic shock, but this

matter merits research as the mechanism of action of levosimendan may contribute to the restoration of more normal coupling.

Future investigations to refine the role of levosimendan in the management of septic shock should address (1) the severity of AHF (a priori, there is a case for reserving levosimendan for patients more likely to benefit from it, such as those with severely reduced LVEF or significant CAD [26,89]); and (2) the timing of the administration (under which heading, matters for attention include investigation of levosimendan as a first-use inotrope for severe SCM in order to optimize its positive cardioprotective effects as intimated from various lines of research, including randomized trials in cardiac surgery that recorded better outcomes with earlier administration [89–92]).

5. Levosimendan and weaning from the ventilator

About 10–20% of intubated patients in ICUs are difficult to wean from mechanical ventilation, resulting in increased morbidity, mortality and healthcare costs [93,94]. Part of this phenomenon may be attributable to the development of diaphragm weakness in intubated patients. Mechanical ventilation results in rapid loss of diaphragmatic force production [95–97]. In one recent study, half of patients (n=185) with diaphragmatic dysfunction failed weaning, half of whom died [98]. In addition, liberation from mechanical ventilation to spontaneous ventilation may dramatically increase left ventricular filling pressure and pulmonary artery pressure, especially in patients with pre-existing cardiac and/or pulmonary comorbidities.

The pathophysiology of muscle weakness in these patients is complex [99,100] but includes muscle fiber atrophy and reduced calcium sensitivity of the contractile proteins [101]. As respiratory muscle troponin resembles cardiac troponin, it is plausible that levosimendan may enhance muscular contractility in the same way that it enhances cardiac contractility. This supposition has support from in vitro data [102], experimental research [103] and a healthy volunteer study [104]. Positive effects were seen in both slow and rapid diaphragm muscle fibers [102,103].

Levosimendan has been compared with dobutamine in difficult-to-wean chronic obstructive pulmonary disease patients [105]. Levosimendan resulted in significantly greater inhibition of spontaneous ventilation-induced congestion caused by a rapid increase in pulmonary artery occlusion pressure. Similarly, mean pulmonary artery pressure increased to a lesser extent with levosimendan than with dobutamine. In a prospective observational study in ventilator-dependent difficult-to-wean ICU patients with diminished LVEF (<40%), levosimendan improved cardiac contractility and oxygenation variables and increased the likelihood of separation from mechanical ventilation [93]. A study entitled the Effects of Levosimendan on Diaphragm Function in Mechanically Ventilated Patients (NCT01721434) coordinated by the University Medical Center, Nijmegen, The Netherlands is currently recruiting.

6. Levosimendan and weaning from extracorporeal membrane oxygenation

Veno-Arterial extracorporeal membrane oxygenation (VA ECMO) is increasingly used for short-term management of refractory CS caused by AMI, myocarditis, cardiac surgical procedures in high-risk patients with reduced LVEF, refractory cardiac arrest and other conditions. In general it is reserved for situations where pharmacological support of the circulation is not able to restore

adequate cardiac output. In cases where there is sufficient recovery of myocardial function during VA-ECMO support, the phase of weaning starts by reducing blood flow through VA ECMO and thus increasing blood flow to the native heart chambers and pulmonary circulation, i.e. increasing the load imposed on both ventricles. In a large observational study, the rate of successful weaning in 4658 patients with CS was reported to be limited to 65.7% [106].

A first report on levosimendan in the context of VA-ECMO weaning showed that pretreatment 24 h before the start of weaning was associated with a 50% reduction in the need for inotropic and/or vasopressor support during or after weaning, as compared with a 100% requirement in the retrospective control group (n=11) ($p<0.003$) [107]. The weaning success rate was significantly higher with levosimendan (83.3% vs. 27.3%; $p=0.0498$); the difference in survival rate was substantial but not statistically significant (66.6% vs. 36.4%).

In a recent retrospective analysis of 240 patients on VA ECMO after cardiovascular surgery, levosimendan was given during the first 24 h of ECMO support in 74.6% of cases [108]. The adjusted hazard ratio (HR) for failure of ECMO weaning with levosimendan was significantly improved versus control (HR 0.41; 95% confidence interval 0.22–0.80; $p=0.008$); furthermore, patients in the levosimendan group experienced lower 30-day mortality ($p=0.016$) and better long-term survival (**Figure 2**). Another study reported improvement in endothelial function after levosimendan infusion in the patients on VA ECMO, together with an improvement in cardiac function (i.e. an increase in cardiac output), facilitating weaning from ECMO [109]. Very recent data show that levosimendan enables weaning from ECLS without increasing norepinephrine requirements when compared with a control group receiving milrinone [110].

Most patients require inotropic drugs to support myocardial contractile function during weaning from VA ECMO and the limited clinical evidence currently available suggests that levosimendan offers some important advantages over other inotropes for this vulnerable period: no increase in myocardial oxygen consumption, a prolonged cardiovascular effect (days) and improvement in endothelial function.

7. Levosimendan in pulmonary hypertension and right ventricular dysfunction

Acute postoperative pulmonary hypertension is a rare but serious event after weaning from cardiopulmonary bypass and must be managed aggressively to avoid right ventricular failure [111,112]. The in-hospital mortality rate is high and may reach 70–75% [113,114]. Similar considerations apply in non-surgical ICUs where right ventricular dysfunction may emerge as a complication of acute respiratory distress syndrome [115].

The thin-walled right ventricle has poor tolerance for acute increases in afterload. Ventricular distension leads to severe compromise of contractility concomitant with an increase in oxygen consumption. Ventricular interdependence then implicates the left ventricle, leading to reduced filling, decreased cardiac output and oxygen delivery and decline in systemic perfusion pressure [116]. The pressure gradient for the perfusion of the right coronary artery drops as aortic pressure decreases and right ventricular pressure increases, leading to right ventricular ischemia [117].)

Augmentation of right ventricular function with inotropic support is central to counteracting this vicious cycle. Levosimendan improves myocardial contractility, with a reduction in pulmonary vascular resistance [118]. In an experimental pressure load-induced model of right ventricular

failure, levosimendan improved right ventricular to pulmonary artery coupling more than dobutamine [119]. The treatment of acute right ventricular failure involves reversing the cause of the increased pulmonary vascular resistance while maintaining adequate MAP. To support adequate systemic arterial tone, a vasopressor is often required, while levosimendan helps to decrease pulmonary vascular resistance and filling pressures.

Investigator-initiated studies have been performed in patients with right ventricular failure. In these, levosimendan reduced increased right ventricular afterload and improved right ventricular contractility and diastolic function [120–123].

A recent meta-analysis demonstrated that levosimendan decreased systolic pulmonary pressure and pulmonary vascular resistance concomitant with an increase in right ventricular ejection fraction in patients suffering from acute right HF [124]. Much of the extant data comes from non-cardiac surgery patients suffering acute onset of pulmonary hypertension and/or right ventricular dysfunction; data on levosimendan in acute right ventricular failure are sparse though encouraging [125].

8. Levosimendan and renal function

Evidence for a renal-protective action of levosimendan in preclinical experiments is persuasive but the clinical dataset supporting a renal-protective effect rests on a limited number of studies, many of them small and characterized by heterogeneities [126]. The results of those studies acquire significance only when pooled in meta-analyses [127–130] but, addressed in that way,

the findings are suggestive of a renal-protective effect of levosimendan in a range of cardiac low-output states that may be pertinent to the ICU setting.

Levosimendan has been compared with dobutamine in 88 patients with HF who required inotropic therapy [131]. Calculated glomerular filtration rate (cGFR) improved in response to levosimendan (0.1–0.2 μg/kg/min, with loading dose at the discretion of individual physicians) but was unchanged in patients who received dobutamine (5 μg/kg/min for at least 6 h, with subsequent dose alteration or extension beyond 24 h as judged necessary in individual cases). Complementary findings emerged from a placebo-controlled study in 66 patients hospitalized for decompensated HF and renal dysfunction, with a statistically significant improvement in cGFR in patients who received levosimendan (12 μg/kg optional loading dose, then continuous infusion at 0.05–0.2 μg/kg/min for 24 h). Peak effect was attained 3 days after a 24-h infusion and the effects persisted for up to 14 days [132]. Two open-label studies also reported reduction of serum creatinine levels in levosimendan-treated patients [133,134]. In a recent randomized study [135] on the effect of levosimendan on renal outcome in 90 cardiac surgery patients with chronic kidney disease and perioperative cardiovascular dysfunction, the authors reported a significant reduction in postoperative acute kidney injury (AKI) and a lower incidence of major complications in the levosimendan arm.

What are the mechanisms behind the clinical observation that levosimendan seems to improve renal function in patients with AHF requiring inotropic support? Inodilators increase cardiac output and also potentially renal blood flow (RBF). It is not immediately evident, however, that an inodilator with renal vasodilating properties also increases GFR: it depends on its effect on

the longitudinal distribution of renal vascular resistance. Thus, theoretically, an inodilator that dilates the preglomerular resistance vessels (afferent arterioles) will, at a certain MAP, increase both RBF and GFR. On the other hand, an inodilator that preferentially causes vasodilation of the postglomerular resistance vessels (efferent arterioles) will increase RBF but cause a fall in GFR, due to a fall in the upstream glomerular hydraulic pressure. Finally, an inodilator that dilates both pre- and postglomerular resistance vessels will induce a pronounced increase in RBF with no change in GFR. Redfors et al. [136] showed in postcardiac surgery patients that low-dose dopamine (2–4 µg/kg/min) induced a pronounced 40–50% increase in RBF with no effect on GFR, suggesting vasodilation of both pre- and postglomerular resistance vessels. Levosimendan, on the other hand, has been shown to increase both RBF and GFR after cardiac surgery, indicating that, in contrast to dopamine, levosimendan improves renal performance by means of preferential preglomerular vasodilation [137] (**Figure 3**). The major goal in the treatment of AKI is to increase GFR. There is, however, a close association between GFR and renal oxygen consumption [138], as any agent that increases GFR will also increase renal oxygen demand. Thus, an ideal inodilator to treat AKI would be one that increases both RBF and GFR. Such an agent will not only increase GFR but will also meet the increased renal metabolic demand by means of increased renal oxygen delivery. Bragadottir et al. [137] showed that the levosimendan-induced increase in GFR did not impair the renal oxygen supply/demand relationship, suggesting that levosimendan could be an interesting agent for treatment of AHF accompanied by impaired renal function in various clinical settings. In a recent double blind randomized clinical trial the same group recently showed that, in patients with chronic heart failure and renal impairment, levosimendan increases glomerular filtration rate to a greater extent

than dobutamine and thus may be the preferred inotropic agent for treating patients with the cardio-renal syndrome [139]

Complementary findings were reported from a placebo-controlled study by Fedele et al. [~~139~~140] in patients with acute decompensated HF and moderate renal impairment (NCT00527059). Yilmaz et al. [126] have speculated on the likely contribution of K_{ATP} channel-opening effects of levosimendan in vascular smooth muscle to a direct renal-protective effect of levosimendan separate from, and additional to, its effects via improved cardiac function and systemic hemodynamics. Observations on the significance of levosimendan-mediated vasodilatation and decongestion have been made by Damman and Voors [~~140~~141].

Diuretic resistance in HF patients is a common problem. One treatment option could be the administration of levosimendan. This might be a good option before the more aggressive implementation of ultrafiltration [~~141~~142].

9. Other settings

Is to be noticed that the HFA-ESC Task Force on Takotsubo syndrome [~~142~~143] advocates levosimendan as the single form of inotropic support in cases of unavailable ECLS. Case reports are encouraging [~~143~~144] and the pathophysiology is conceptually a good fit to the properties of levosimendan.

10. Conclusions

Levosimendan has been demonstrated to have potential utility in a range of critical illness scenarios. It must be acknowledged, however, that in each sphere of application the evidence is incomplete or indicative rather than conclusive and further clinical evaluation will be needed to substantiate the case for levosimendan and to refine the patient categories and dosage schedules likely to be associated with the greatest clinical benefit .

Having levosimendan a vasodilatory effect, its dosage should be guided in part by following the blood pressure of the patient (as recommended by the indication for use), with bolus omitted or used only if SBP is ≥100 mm Hg [145] (see **Box 3**). Meta-analysis of 45 randomized controlled trials in cardiac surgery or cardiology identifies an infusion rate range of 0.05–0.2 $mg \times kg^{-1} \times min^{-1}$, with some indications that both lower rates (≤ 0.1 $mg \times kg^{-1} \times min^{-1}$) and omission of bolus dose may confer greater long-term survival advantages over higher doses and use of bolus **[**146]. The presence of a long-lived metabolite is associated with the persistence of the hemodynamic effects of levosimendan [147] 7-10 days after a single 24-hour infusion of levosimendan. The inodilator levosimendan is mainly used for its hemodynamic effects, and the longer action of its active metabolite is fully consistent with the pharmacologic effects observed in the beginning of the treatment: no increase in the rate of adverse events was observed after the 24-hour infusion of levosimendan [148].

The regulatory Phase IIb-III clinical trials program on the efficacy and safety of levosimendan in acute heart failure completed in 2005 (see complete trial list in Pollesello et al. [149]) did not give an unequivocal answer to the question whether the short term use of

levosimendan lowers long term mortality in patients hospitalized for decompensated acute heart failure irrespectively to its etiology and to the use of co-medications during the pre-, peri-, and post-acute phase. Some trials showed a significant improvement in survival, some (the larger ones) not, but the bulk of evidence did overall support the efficacy and safety of the drug, and a market authorization was granted in over 60 countries, with the notable exception of the U.S.A. and the U.K. The regulatory studies included a broad variability of patients, both as it regards the etiologies (e.g. de novo vs chronic decompensated HF), the monitoring (e.g. invasively vs non-invasively), the time of treatment (e.g. early during hospitalization vs late), and the co-medications (e.g. beta-blockade vs non beta-blockade). When more homogeneous groups of patients are considered (see analysis by Kivikko et al. [150]) the short term effects of levosimendan on symptoms, hemodynamics, and neurohormons, are accompanied to a significant long-term effect on survival. As it regards the clinical studies in the ICU field, the same pattern can be seen when comparing the large LEOPARDS study [37] to the many previous smaller studies on the use of levosimendan in septic shock [151]: when the patients are poorly defined, the results are so spread that not any statistical significance can be reached. Therefrom originates the conundrum: in the field of ICU, the large studies needed for 'evidence based medicine' necessarily include a broad spectrum of patients and the effects of drugs can be easily masked in the statistical analyses, while smaller (often monocentric) studies can spot significant positive drugs effects due to the good selection of patients, but their results will remain necessarily limited. We hereby propose possible solutions for a way out.

Central to future investigations must be the identification of robust and relevant endpoints. An improvement in survival/mortality may be plausible in cases where levosimendan substitutes for an adrenergic inotrope with a documented propensity to increase mortality. In other settings, however, it is not obvious that a mortality gain can be assumed nor is it certain that any such gain, welcome as it would be, would be the most pertinent measurement of any treatment effect. It is, moreover, unclear how far into the future any survival benefit from a short-term intervention in what is likely to be a complex and multifaceted medical crisis should reasonably be expected to extend. None of the conventional adrenergic inotropic drugs have in fact been associated with improvements in hard endpoints such as mortality and there are many indications to the contrary. The reported experience of Distelmaier et al. [108] **(Figure 2)** is encouraging with regard to the prospect of a long-term advantage in the sphere of weaning from ECMO but may not be similarly applicable in other situations and is in any case in need of corroboration.

We consider, for these reasons, that an overemphasis on crude mortality may not be the most informative approach to future clinical trials of levosimendan. We are inclined towards the position of Schumann and colleagues [72], who have advocated the evaluation of EGDT in CS and low-cardiac output syndrome, arguing that refining the best therapeutic strategy is more constructive than trying to identify the 'best' drug for hemodynamic support. Similarly, identifying the most effective regimen for, say, weaning from ECMO or the management of pulmonary hypertension needs to take a wider view of the issue than simply focusing too closely on the impact of a single intervention perhaps delivered for a short period of time. The adoption of hierarchical endpoints in clinical trials of levosimendan in HF (e.g. LEODOR; NCT03437226) is an innovation that may also find applications in future clinical trials in the

ICU setting and may enable a more nuanced appraisal of the impact of levosimendan in those situations.

~~The concepts of 'enriched enrollment', ' omics profile feeding new biomarkers' and 'accurate prognostication' are key to precision medicine and may be expected to contribute to improving the power, robustness and information yield from future trials [144].~~

Declarations

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References

1. Papp Z, Édes I, Fruhwald S, De Hert SG, Salmenperä M, Leppikangas H, Mebazaa A, Landoni G, Grossini E, Caimmi P, Morelli A, Guarracino F, Schwinger RH, Meyer S, Algotsson L, Wikström BG, Jörgensen K, Filippatos G, Parissis JT, González MJ, Parkhomenko A, Yilmaz MB, Kivikko M, Pollesello P, Follath F. Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol. 2012;159:82-7.

2. Nieminen MS, Fruhwald S, Heunks LM, Suominen PK, Gordon AC, Kivikko M, Pollesello P. Levosimendan: current data, clinical use and future development. Heart Lung Vessel. 2013;5:227-45.

3. Pollesello P, Ovaska M, Kaivola J, Tilgmann C, Lundström K, Kalkkinen N, Ulmanen I, Nissinen E, Taskinen J. Binding of a new Ca2+ sensitizer, levosimendan, to recombinant human cardiac troponin C. A molecular modelling, fluorescence probe, and proton nuclear magnetic resonance study. J Biol Chem. 1994;269:28584-90.

4. Pääkkönen K, Annila A, Sorsa T, Pollesello P, Tilgmann C, Kilpeläinen I, Karisola P, Ulmanen I, Drakenberg T. Solution structure and main chain dynamics of the regulatory domain (Residues 1-91) of human cardiac troponin C. J Biol Chem. 1998;273:15633-8.

5. Sorsa T, Heikkinen S, Abbott MB, Abusamhadneh E, Laakso T, Tilgmann C, Serimaa R, Annila A, Rosevear PR, Drakenberg T, Pollesello P, Kilpelainen I. Binding of levosimendan, a calcium sensitizer, to cardiac troponin C. J Biol Chem. 2001;276:9337-43.

6. Kaheinen P, Pollesello P, Levijoki J, Haikala H. Effects of levosimendan and milrinone on oxygen consumption in isolated guinea-pig heart. J Cardiovasc Pharmacol. 2004;43:555-61.

7. Eriksson O, Pollesello P, Haikala H. Effect of levosimendan on balance between ATP production and consumption in isolated perfused guinea-pig heart before ischemia or after reperfusion. J Cardiovasc Pharmacol. 2004;44:316-21.

8. Ukkonen H, Saraste M, Akkila J, Knuuti MJ, Lehikoinen P, Någren K, Lehtonen L, Voipio-Pulkki LM. Myocardial efficiency during calcium sensitization with levosimendan: a noninvasive study with positron emission tomography and echocardiography in healthy volunteers. Clin Pharmacol Ther. 1997;61:596-607.

9. Ukkonen H, Saraste M, Akkila J, Knuuti J, Karanko M, Iida H, Lehikoinen P, Någren K, Lehtonen L, Voipio-Pulkki LM. Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther. 2000;68:522-31.

10. Lilleberg J, Nieminen MS, Akkila J, Heikkilä L, Kuitunen A, Lehtonen L, Verkkala K, Mattila S, Salmenperä M. Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. Eur Heart J. 1998;19:660-8.

11. Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N. The novel calcium sensitizer levosimendan activates the ATP-sensitive K+ channel in rat ventricular cells. J Pharmacol Exp Ther. 1997;283:375-83.

12. Pataricza J, Krassói I, Höhn J, Kun A, Papp JG. Functional role of potassium channels in the vasodilating mechanism of levosimendan in porcine isolated coronary artery. Cardiovasc Drugs Ther. 2003;17:115-21.

13. De Witt BJ, Ibrahim IN, Bayer E, Fields AM, Richards TA, Banister RE, Kaye AD. An analysis of responses to levosimendan in the pulmonary vascular bed of the cat. Anesth Analg. 2002;94:1427-33.

14. Gruhn N, Nielsen-Kudsk JE, Theilgaard S, Bang L, Olesen SP, Aldershvile J. Coronary vasorelaxant effect of levosimendan, a new inodilator with calcium-sensitizing properties. J Cardiovasc Pharmacol. 1998;31:741-9.

15. Kaheinen P, Pollesello P, Levijoki J, Haikala H. Levosimendan increases diastolic coronary flow in isolated guinea-pig heart by opening ATP-sensitive potassium channels. J Cardiovasc Pharmacol. 2001;37:367-74.

16. Erdei N, Papp Z, Pollesello P, Edes I, Bagi Z. The levosimendan metabolite OR-1896 elicits vasodilation by activating the K(ATP) and BK(Ca) channels in rat isolated arterioles. Br J Pharmacol. 2006;148:696-702.

17. Höhn J, Pataricza J, Petri A, Tóth GK, Balogh A, Varró A, Papp JG. Levosimendan interacts with potassium channel blockers in human saphenous veins. Basic Clin Pharmacol Toxicol. 2004;94:271-3.

18. Kopustinskiene DM, Pollesello P, Saris NE. Potassium-specific effects of levosimendan on heart mitochondria. Biochem Pharmacol. 2004;68:807-12.

19. Pollesello P, Papp Z. The cardioprotective effects of levosimendan: preclinical and clinical evidence. J Cardiovasc Pharmacol. 2007;50:257-63.

20. Tritapepe L, De Santis V, Vitale D, Guarracino F, Pellegrini F, Pietropaoli P, Singer M. Levosimendan pre-treatment improves outcomes in patients undergoing coronary artery bypass graft surgery. Br J Anaesth. 2009;102:198-204.

21. Raasmaja A, Talo A, Haikala H, Nissinen E, Lindén IB, Pohto P. Biochemical properties of OR-1259: a positive inotropic and vasodilatory compound with an antiarrhythmic effect. Adv Exp Med Biol. 1992;311:423.

22. Lilleberg JM, Sundberg S, Leikola-Pelho T, Nieminen MS. Hemodynamic effects of the novel cardiotonic drug simendan: echocardiographic assessment in healthy volunteers. Cardiovasc Drugs Ther. 1994;8:263-9.

23. Mebazaa A, Nieminen MS, Filippatos GS, Cleland JG, Salon JE, Thakkar R, Padley RJ, Huang B, Cohen-Solal A. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. Eur J Heart Fail. 2009;11:304-11.

24. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L; Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet. 2002;360:196-202.

25. Moiseyev VS, Põder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, Kobalava ZD, Lehtonen LA, Laine T, Nieminen MS, Lie KI; RUSSLAN Study Investigators. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J. 2002;23:1422-32.

26. Sanfilippo F, Knight JB, Scolletta S, Santonocito C, Pastore F, Lorini FL, Tritapepe L, Morelli A, Arcadipane A. Levosimendan for patients with severely reduced left ventricular systolic function and/or low cardiac output syndrome undergoing cardiac surgery: a systematic review and meta-analysis. Crit Care. 2017;21:252.

27. Guarracino F, Heringlake M, Cholley B, Bettex D, Bouchez S, Lomivorotov VV, Rajek A, Kivikko M, Pollesello P. Use of levosimendan in cardiac surgery: An update after the LEVO-CTS, CHEETAH, and LICORN trials in the light of clinical practice. J Cardiovasc Pharmacol. 2018;71:1-9.

28. Farmakis D, Alvarez J, Gal TB, Brito D, Fedele F, Fonseca C, Gordon AC, Gotsman I, Grossini E, Guarracino F, Harjola VP, Hellman Y, Heunks L, Ivancan V, Karavidas A, Kivikko M, Lomivorotov V, Longrois D, Masip J, Metra M, Morelli A, Nikolaou M, Papp Z, Parkhomenko A, Poelzl G, Pollesello P, Ravn HB, Rex S, Riha H, Ricksten SE, Schwinger RHG, Vrtovec B, Yilmaz MB, Zielinska M, Parissis J. Levosimendan beyond inotropy and

acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper. Int J Cardiol. 2016;222:303-12

29. Balzer F, Treskatsch S, Spies C, Sander M, Kastrup M, Grubitzsch H, Wernecke KD, Braun JP. Early administration of levosimendan is associated with improved kidney function after cardiac surgery—a retrospective analysis. J Cardiothorac Surg. 2014;9:167.
30. Alvarez J, Baluja A, Selas S, Otero P, Rial M, Veiras S, Caruezo V, Taboada M, Rodriguez I, Castroagudin J, Tome S, Rodriguez A, Rodriguez J. A comparison of dobutamine and levosimendan on hepatic blood flow in patients with a low cardiac output state after cardiac surgery: a randomised controlled study. Anaesth Intensive Care. 2013;41:719-27.
31. Brunner SN, Bogert NV, Schnitzbauer AA, Juengel E, Moritz A, Werner I, Kornberger A, Beiras-Fernandez A. Levosimendan protects human hepatocytes from ischemia-reperfusion injury. PLoS One. 2017;12:e0187839.
32. Gallagher KM, O'Neill S, Harrison EM, Ross JA, Wigmore SJ, Hughes J. Recent early clinical drug development for acute kidney injury. Expert Opin Investig Drugs. 2017;26:141-54.
33. Varvarousi G, Xanthos T, Sarafidou P, Katsioula E, Georgiadou M, Eforakopoulou M, Pavlou H. Role of levosimendan in the management of subarachnoid hemorrhage. Am J Emerg Med. 2016;34:298-306.
34. Wang X, Li S. Effect of small-dose levosimendan on mortality rates and organ functions in Chinese elderly patients with sepsis. Clin Intervent Aging. 2017;12:917-21.
35. Wang X, Ma S, Liu Y, Xu W, Li Z. Effects and mechanism analysis of combined infusion by levosimendan and vasopressin on acute lung injury in rats septic shock. Cell Biochem Biophys. 2014;70:1639-45.

36. Belletti A, Benedetto U, Biondi-Zoccai G, Leggieri C, Silvani P, Angelini GD, Zangrillo A, Landoni G. The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. J Crit Care. 2017;37:91-8.

37. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RM, Santhakumaran S, Mason AJ, Cross M, Al-Beidh F, Best-Lane J, Brealey D, Nutt CL, McNamee JJ, Reschreiter H, Breen A, Liu KD, Ashby D. Levosimendan for the prevention of acute organ dysfunction in sepsis. N Engl J Med. 2016;375:1638-48.

38. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. Consensus on circulatory shock and hemodynamic monitoring. Task Force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40:1795-815.

39. Vincent J.-L, De Backer D. Circulatory shock. N Engl J Med. 2013;369:1726-34.

40. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129-200.

41. Mebazaa A, Tolppanen H, Mueller C, Lassus J, DiSomma S, Baksyte G, Cecconi M, Choi DJ, Cohen Solal A, Christ M, Masip J, Arrigo M, Nouira S, Ojji D, Peacock F, Richards M, Sato N, Sliwa K, Spinar J, Thiele H, Yilmaz MB, Januzzi J. Acute heart failure and

cardiogenic shock: a multidisciplinary practical guidance. Intensive Care Med. 2016;42:147-63.

42. Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, Cheng ML, Wynne J; ADHERE Scientific Advisory Committee and Investigators; ADHERE Study Group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications. J Am Coll Cardiol. 2005;46:57-64.
43. Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolaou M, Boas FV, Delgado JF, Follath F. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. Intensive Care Med. 2010;37:290-301.
44. Mebazaa A, Motiejunaite J, Gayat E, Crespo-Leiro MG, Lund LH, Maggioni AP, Chioncel O, Akiyama E, Harjola VP, Seferovic P, Laroche C, Julve MS, Roig E, Ruschitzka F, Filippatos G; ESC Heart Failure Long-Term Registry Investigators. Long-term safety of intravenous cardiovascular agents in acute heart failure: results from the European Society of Cardiology Heart Failure Long-Term Registry. Eur J Heart Fail. 2018;20:332-41.
45. Tarvasmäki T, Lassus J, Varpula M, Sionis A, Sund R, Køber L, Spinar J, Parissis J, Banaszewski M, Silva Cardoso J, Carubelli V, Di Somma S, Mebazaa A, Harjola VP; CardShock study investigators. Current real-life use of vasopressors and inotropes in cardiogenic shock—adrenaline use is associated with excess organ injury and mortality. Crit Care. 2016;20:208.
46. Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, Davies A, Delaney A, Harrison DA, Holdgate A, Howe B, Huang DT, Iwashyna T, Kellum JA, Peake SL, Pike F, Reade MC, Rowan KM, Singer M, Webb SA, Weissfeld LA, Yealy DM, Young JD. A

systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med. 2015;41:1549-60.

47. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary management of cardiogenic shock: A scientific statement from the American Heart Association. Circulation. 2017;136:e232-68.

48. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45:486-552.

49. Heusch G. Heart rate in the pathophysiology of coronary blood flow and myocardial ischaemia: benefit from selective bradycardic agents. Br J Pharmacol. 2008;153:1589-601.

50. Schulz R, Rose J, Martin C, Brodde OE, Heusch G. Development of short-term myocardial hibernation. Its limitation by the severity of ischemia and inotropic stimulation. Circulation. 1993;88:684-95.

51. Beohar N, Erdogan AK, Lee DC, Sabbah HN, Kern MJ, Teerlink J, Bonow RO, Gheorghiade M. Acute heart failure syndromes and coronary perfusion. J Am Coll Cardiol. 2008;52:13-16.

52. Duncker DJ, Koller A, Merkus D, Canty JM Jr. Regulation of coronary blood flow in health and ischemic heart disease. Prog Cardiovasc Dis. 2015;57:409-22.

53. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo syndrome. Circulation. 2017;135:2426-41.

54. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. Crit Care Med. 2007;35:1599-608.

55. Tacon CL, McCaffrey J, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. Intensive Care Med. 2012;38:359-67.

56. Schmittinger CA, Torgersen C, Luckner G, Schröder DC, Lorenz I, Dünser MW. Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. Intensive Care Med. 2012;38:950-8.

57. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G; European Society of Cardiology; European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of

the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12:423-33.

58. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, Gheorghiade M, O'Connor CM; OPTIME-CHF Investigators. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol. 2003;41:997-1003.
59. Nielsen DV, Torp-Pedersen C, Skals RK, Gerds TA, Karaliunaite Z, Jakobsen CJ. Intraoperative milrinone versus dobutamine in cardiac surgery patients: a retrospective cohort study on mortality. Crit Care. 2018;22:51.
60. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779-89.
61. Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med. 2011;39:450-5.
62. Singer M. Catecholamine treatment for shock—equally good or bad? Lancet. 2007;370:636-7.
63. Andreis DT, Singer M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. Intensive Care Med. 2016;42:1387-97.
64. Coquerel D, Sainsily X, Dumont L, Sarret P, Marsault É, Auger-Messier M, Lesur O. The apelinergic system as an alternative to catecholamines in low-output septic shock. Crit Care. 2018;22:10.

65. He X, Su F, Taccone FS, Laporte R, Kjølbye AL, Zhang J, Xie K, Moussa MD, Reinheimer TM, Vincent JL. A selective V(1A) receptor agonist, selepressin, is superior to arginine vasopressin and to norepinephrine in ovine septic shock. Crit Care Med. 2016;44:23-31.

66. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, McCurdy MT, Boldt DW, Chock S, Young PJ, Krell K, Wunderink RG, Ostermann M, Murugan R, Gong MN, Panwar R, Hästbacka J, Favory R, Venkatesh B, Thompson BT, Bellomo R, Jensen J, Kroll S, Chawla LS, Tidmarsh GF, Deane AM; ATHOS-3 Investigators. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med. 2017;377:419-30.

67. Reynold HR, Hochmann JS. Cardiogenic shock: current concepts and improving outcomes. Circulation. 2008;117:686-97.

68. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.

69. García-González MJ, Domínguez-Rodríguez A, Ferrer-Hita JJ, Abreu-González P, Muñoz MB. Cardiogenic shock after primary percutaneous coronary intervention: Effects of levosimendan compared with dobutamine on haemodynamics. Eur J Heart Fail. 2006;8:723-8.

70. Williams SG, Wright DJ, Tan LB. Management of cardiogenic shock complicating acute myocardial infarction: towards evidence based medical practice. Heart. 2000;83:621-6.

71. Fuhrmann JT, Schmeisser A, Schulze MR, Wunderlich C, Schoen SP, Rauwolf T, Weinbrenner C, Strasser RH. Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. Crit Care Med. 2008;36:2257-66.

72. Schumann J, Henrich EC, Strobl H, Prondzinsky R, Weiche S, Thiele H, Werdan K, Frantz S, Unverzagt S. Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome. Cochrane Database Syst Rev. 2018;1:CD009669.

73. Jörgensen K, Bech-Hanssen O, Houltz E, Ricksten SE. Effects of levosimendan on left ventricular relaxation and early filling at maintained preload and afterload conditions after aortic valve replacement for aortic stenosis. Circulation. 2008;117:1075-81.

74. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10.

75. Beesley SJ, Weber G, Sarge T, Nikravan S, Grissom CK, Lanspa MJ, Shahul S, Brown SM. Septic cardiomyopathy. Crit Care Med. 2018;46:625-34.

76. Suzuki T, Suzuki Y, Okuda J, Kurazumi T, Suhara T, Ueda T, Nagata H, Morisaki H. Sepsis-induced cardiac dysfunction and β-adrenergic blockade therapy for sepsis. J Intensive Care. 2017;5:22.

77. Wu LL, Yang SL, Yang RC, Hsu HK, Hsu C, Dong LW, Liu MS. G protein and adenylate cyclase complex-mediated signal transduction in the rat heart during sepsis. Shock. 2003;19:533-7.

78. Rudiger A. Beta-block the septic heart. Crit Care Med. 2010;38:S608-12.

79. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, Orecchioni A, D'Egidio A, D'Ippoliti F, Raffone C, Venditti M, Guarracino F, Girardis M, Tritapepe L, Pietropaoli P, Mebazaa A, Singer M. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock. JAMA. 2013;310:1683-91.

80. Wang Q, Yokoo H, Takashina M, Sakata K, Ohashi W, Abedelzaher LA, Imaizumi T, Sakamoto T, Hattori K, Matsuda N, Hattori Y. Anti-inflammatory profile of levosimendan in cecal ligation-induced septic mice and in lipopolysaccharide-stimulated macrophages. Crit Care Med. 2015;43:e508-20.

81. Tsao CM, Li KY, Chen SJ, Ka SM, Liaw WJ, Huang HC, Wu CC. Levosimendan attenuates multiple organ injury and improves survival in peritonitis-induced septic shock: studies in a rat model. Crit Care. 2014;18:652.

82. Morelli A, De Castro S, Teboul JL, Singer M, Rocco M, Conti G, De Luca L, Di Angelantonio E, Orecchioni A, Pandian NG, Pietropaoli P. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med. 2005;31:638-44.

83. Creteur J, Bouckaert Y, Mélot C, Vincent JL. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med. 2006;32:790; author reply 791-2.

84. Morelli A, Donati A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V, Landoni G, Pelaia P, Pietropaoli P, Van Aken H, Teboul JL, Ince C, Westphal M. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. Crit Care. 2010;14:R232.

85. Torraco A, Carrozzo R, Piemonte F, Pastore A, Tozzi G, Verrigni D, Assenza M, Orecchioni A, D'Egidio A, Marraffa E, Landoni G, Bertini E, Morelli A. Effects of levosimendan on mitochondrial function in patients with septic shock: a randomized trial. Biochimie. 2014;102:166-73.

86. Hajjej Z, Meddeb B, Sellami W, Labbene I, Morelli A, Ferjani M. Effects of levosimendan on cellular metabolic alterations in patients with septic shock: A randomized controlled pilot study. Shock. 2017;48:307-12.

87. Zangrillo A, Putzu A, Monaco F, Oriani A, Frau G, De Luca M, Di Tomasso N, Bignami E, Lomivorotov V, Likhvantsev V, Landoni G. Levosimendan reduces mortality in patients with severe sepsis and septic shock: A meta-analysis of randomized trials. J Crit Care. 2015;30:908-13.

88. Guarracino F, Ferro B, Morelli A, Bertini P, Baldassarri R, Pinsky MR. Ventriculoarterial decoupling in human septic shock. Crit Care. 2014;18:R80.

89. Mehta RH, Leimberger JD, van Diepen S, Meza J, Wang A, Jankowich R, Harrison RW, Hay D, Fremes S, Duncan A, Soltesz EG, Luber J, Park S, Argenziano M, Murphy E, Marcel R, Kalavrouziotis D, Nagpal D, Bozinovski J, Toller W, Heringlake M, Goodman SG, Levy JH, Harrington RA, Anstrom KJ, Alexander JH; LEVO-CTS Investigators. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. N Engl J Med. 2017;376:2032-42.

90. du Toit EF, Genis A, Opie LH, Pollesello P, Lochner A. A role for the RISK pathway and K ATP channels in pre- and post-conditioning induced by levosimendan in the isolated guinea pig heart. Br J Pharmacol. 2008;154:41-50.

91. Kivikko M, Pollesello P, Tarvasmäki T, Sarapohja T, Nieminen MS, Harjola VP. Effect of baseline characteristics on mortality in the SURVIVE trial on the effect of levosimendan vs dobutamine in acute heart failure: Sub-analysis of the Finnish patients. Int J Cardiol. 2016;215:26-31.

92. Levin R, Degrange M, Del Mazo C, Tanus E, Porcile R. Preoperative levosimendan decreases mortality and the development of low cardiac output in high-risk patients with severe left ventricular dysfunction undergoing coronary artery bypass grafting with cardiopulmonary bypass. Exp Clin Cardiol. 2012;17:125-30.

93. Sterba M, Banerjee A, Mudaliar Y. Prospective observational study of levosimendan and weaning of difficult-to-wean ventilator dependent intensive care patients. Crit Care Resusc. 2008;10:182-6.

94. Goligher EC, Dres M, Fan E Rubenfeld GD, Scales DC, Herridge MS, Vorona S, Sklar MC, Rittayamai N, Lanys A, Murray A, Brace D, Urrea C, Reid WD, Tomlinson G, Slutsky AS, Kavanagh BP, Brochard LJ, Ferguson ND. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. Am J Respir Crit Care Med. 2018;197:204-13.

95. Demoule A, Molinari N, Jung B, Prodanovic H, Chanques G, Matecki S, Mayaux J, Similowski T, Jaber S. Patterns of diaphragm function in critically ill patients receiving prolonged mechanical ventilation: a prospective longitudinal study. Ann Intensive Care. 2016;6:75.

96. Dot I, Pérez-Teran P, Samper MA, Masclans JR. Diaphragm dysfunction in mechanically ventilated patients. Arch Bronconeumol. 2017;53:150-6.

97. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care. 2010;14:R127.

98. Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, Albaladejo P, Chanques G, Molinari N, Jaber S. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med. 2016;42:853-61.

99. Tang H, Smith IJ, Hussain SN, Goldberg P, Lee M, Sugiarto S, Godinez GL, Singh BK, Payan DG, Rando TA, Kinsella TM, Shrager JB. The JAK-STAT pathway is critical in ventilator-induced diaphragm dysfunction. Mol Med. 2015;20:579-89.

100. Larsson L, Friedrich O. Critical illness myopathy (CIM) and ventilator-induced diaphragm muscle dysfunction (VIDD): acquired myopathies affecting contractile proteins. Compr Physiol. 2016;7:105-11.

101. Ottenheijm CA, Heunks LM, Sieck GC, Zhan WZ, Jansen SM, Degens H, de Boo T, Dekhuijzen PN. Diaphragm dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172:200-5.

102. van Hees HW, Dekhuijzen PN, Heunks LM. Levosimendan enhances force generation of diaphragm muscle from patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;179:41-7.

103. van Hees HW, Andrade Acuna G, Linkels M, Dekhuijzen PN, Heunks LM. Levosimendan improves calcium sensitivity of diaphragm muscle fibres from a rat model of heart failure. Br J Pharmacol. 2011;162:566-73.

104. Doorduin J, Sinderby CA, Beck J, Stegeman DF, van Hees HW, van der Hoeven JG, Heunks LM. The calcium sensitizer levosimendan improves human diaphragm function. Am J Respir Crit Care Med. 2012;185:90-5.

105. Ouanes-Besbes L, Ouanes I, Dachraoui F, Dimassi S, Mebazaa A, Abroug F. Weaning difficult-to-wean chronic obstructive pulmonary disease patients: a pilot study comparing initial hemodynamic effects of levosimendan and dobutamine. J Crit Care. 2011;26:15-21.

106. Aso S, Matsui H, Fushimi K, Yasunaga H. In-hospital mortality and successful weaning from venoarterial extracorporeal membrane oxygenation: analysis of 5,263 patients using a national inpatient database in Japan. Crit Care. 2016;20:80.

107. Affronti A, di Bella I, Carino D, Ragni T. Levosimendan may improve weaning outcomes in venoarterial ECMO patients. ASAIO J. 2013;59:554-7.

108. Distelmaier K, Roth C, Schrutka L, Binder C, Steinlechner B, Heinz G, Lang IM, Maurer G, Koinig H, Niessner A, Hülsmann M, Speidl W, Goliasch G. Beneficial effects of levosimendan on survival in patients undergoing extracorporeal membrane oxygenation after cardiovascular surgery. Br J Anaesth. 2016;117:52-8.

109. Sangalli F, Avalli L, Laratta M, Formica F, Maggioni E, Caruso R, Cristina Costa M, Guazzi M, Fumagalli R. Effects of levosimendan on endothelial function and hemodynamics during weaning from veno-arterial extracorporeal life support. J Cardiothorac Vasc Anesth. 2016;30:1449-53.

110. Jacky A, Rudiger A, Krüger B, Wilhelm MJ, Paal S, Seifert B, Spahn DR, Bettex D. Comparison of levosimendan and milrinone for ECLS weaning in patients after cardiac surgery—a retrospective before and after study. *J Cardiothorac Vasc Anesth. 2018*; doi:10.1053/j.jvca.2018.04.019.

111. Gordon C, Collard CD, Pan W. Intraoperative management of pulmonary hypertension and associated right heart failure. Curr Opin Anaesthesiol. 2010;23:49-56.

112. Lahm T, McCaslin CA, Wozniak TC, Ghumman W, Fadl YY, Obeidat OS, Schwab K, Meldrum DR. Medical and surgical treatment of acute right ventricular failure. J Am Coll Cardiol. 2010;56:1435-46.

113. Kaul TK, Fields BL. Postoperative acute refractory right ventricular failure: incidence, pathogenesis, management and prognosis. Cardiovasc Surg. 2000;8:1-9.

114. Ochiai Y, McCarthy PM, Smedira NG, Banbury MK, Navia JL, Feng J, Hsu AP, Yeager ML, Buda T, Hoercher KJ, Howard MW, Takagaki M, Doi K, Fukamachi K. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. Circulation. 2002;106(12 Suppl 1):I198-202.

115. Zochios V, Parhar K, Tunnicliffe W, Roscoe A, Gao F. The right ventricle in ARDS. Chest. 2017;152:181-93.

116. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Crit Care. 2010;14:R169.

117. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: hemodynamic and biochemical correlations. Circulation. 1981;63:87-95.

118. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, Hutchins S, Leier CV, LeJemtel TH, Loh E, Nicklas J, Ogilby D, Singh BN, Smith W. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. Circulation. 2000;102:2222-7.

119. Kerbaul F, Rondelet B, Demester JP, Fesler P, Huez S, Naeije R, Brimioulle S. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. Crit Care Med. 2006;34:2814-9.

120. Parissis JT, Paraskevaidis I, Bistola V, Farmakis D, Panou F, Kourea K, Nikolaou M, Filippatos G, Kremastinos D. Effects of levosimendan on right ventricular function in patients with advanced heart failure. Am J Cardiol. 2006;98:1489-92.

121. Poelzl G, Zwick RH, Grander W, Metzler B, Jonetzko P, Frick M, Ulmer H, Pachinger O, Roithinger FX. Safety and effectiveness of levosimendan in patients with predominant right heart failure. Herz. 2008;33:368-73.

122. Russ MA, Prondzinsky R, Carter JM, Schlitt A, Ebelt H, Schmidt H, Lemm H, Heinroth K, Soeffker G, Winkler M, Werdan K, Buerke M. Right ventricular function in myocardial infarction complicated by cardiogenic shock: Improvement with levosimendan. Crit Care Med. 2009;37:3017-23.

123. Morelli A, Teboul JL, Maggiore SM, Vieillard-Baron A, Rocco M, Conti G, De Gaetano A, Picchini U, Orecchioni A, Carbone I, Tritapepe L, Pietropaoli P, Westphal M. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study. Crit Care Med. 2006;34:2287-93.

124. Qiu J, Jia L, Hao Y, Huang S, Ma Y, Li X, Wang M, Mao Y. Efficacy and safety of levosimendan in patients with acute right heart failure: A meta-analysis. Life Sci. 2017;184:30-6.

125. Guerrero-Orriach JL, Ariza-Villanueva D, Florez-Vela A, Garrido-Sánchez L, Moreno-Cortés MI, Galán-Ortega M, Ramírez-Fernández A, Alcaide Torres J, Fernandez CS, Navarro Arce I, Melero-Tejedor JM, Rubio-Navarro M, Cruz-Mañas J. Cardiac, renal, and

neurological benefits of preoperative levosimendan administration in patients with right ventricular dysfunction and pulmonary hypertension undergoing cardiac surgery: evaluation with two biomarkers neutrophil gelatinase-associated lipocalin and neuronal enolase. Ther Clin Risk Manag. 2016;12:623-30.

126. Yilmaz MB, Grossini E, Silva Cardoso JC, Édes I, Fedele F, Pollesello P, Kivikko M, Harjola VP, Hasslacher J, Mebazaa A, Morelli A, le Noble J, Oldner A, Oulego Erroz I, Parissis JT, Parkhomenko A, Poelzl G, Rehberg S, Ricksten SE, Rodríguez Fernández LM, Salmenperä M, Singer M, Treskatsch S, Vrtovec B, Wikström G. Renal effects of levosimendan: a consensus report. Cardiovasc Drugs Ther. 2013;27:581-90.

127. Pisano A, Monti G, Landoni G. Levosimendan: new indications and evidence for reduction in perioperative mortality? Curr Opin Anaesthesiol. 2016;29:454-61.

128. Bove T, Matteazzi A, Belletti A, Paternoster G, Saleh O, Taddeo D, Dossi R, Greco T, Bradic N, Husedzinovic I, Nigro Neto C, Lomivorotov VV, Calabrò MG. Beneficial impact of levosimendan in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. Heart Lung Vessel. 2015;7:35-46.

129. Zhou C, Gong J, Chen D, Wang W, Liu M, Liu B. Levosimendan for prevention of acute kidney injury after cardiac surgery: A meta-analysis of randomized controlled trials. Am J Kidney Dis. 2016;67:408-416.

130. Knezevic I, Poglajen G, Hrovat E, Oman A, Pintar T, Wu JC, Vrtovec B, Haddad F. The effects of levosimendan on renal function early after heart transplantation: results from a pilot randomized trial. Clin Transplant. 2014;28:1105-11.

131. Yilmaz MB, Yalta K, Yontar C, Karadas F, Erdem A, Turgut OO, Yilmaz A, Tandogan I. Levosimendan improves renal function in patients with acute decompensated heart failure: comparison with dobutamine. Cardiovasc Drugs Ther. 2007;21:431-5.

132. Hou ZQ, Sun ZX, Su CY, Tan H, Zhong X, Hu B, Zhou Y, Shang DY. Effect of levosimendan on estimated glomerular filtration rate in hospitalized patients with decompensated heart failure and renal dysfunction. Cardiovasc Ther. 2013;31:108-14.

133. Zemljic G, Bunc M, Yazdanbakhsh AP, Vrtovec B. Levosimendan improves renal function in patients with advanced chronic heart failure awaiting cardiac transplantation. J Card Fail. 2007;13:417-21.

134. Silva-Cardoso J, Ferreira J, Oliveira-Soares A, Martins-de-Campos J, Fonseca C, Lousada N, Ilídio-Moreira J, Rabaçal C, Damasceno A, Amorim S, Seabra-Gomes R, Ferreira R, Abreu-Lima C; PORTLAND Investigators. Effectiveness and safety of levosimendan in clinical practice. Rev Port Cardiol. 2009;28:143-53.

135. Zangrillo A, Alvaro G, Belletti A, Pisano A, Brazzi L, Calabrò MG, Guarracino F, Bove T, Grigoryev EV, Monaco F, Boboshko VA, Likhvantsev VV, Scandroglio AM, Paternoster G, Lembo R, Frassoni S, Comis M, Pasyuga VV, Navalesi P, Lomivorotov VV; CHEETAH Study Group. Effect of levosimendan on renal outcome in cardiac surgery patients with chronic kidney disease and perioperative cardiovascular dysfunction: a substudy of a multicenter randomized trial. J Cardiothorac Vasc Anesth. 2018; doi:10.1053/j.jvca.2018.02.039.

136. Redfors B, Bragadottir G, Sellgren J, Swärd K, Ricksten SE. Dopamine increases renal oxygenation: a clinical study in post-cardiac surgery patients. Acta Anaesthesiol Scand. 2010;54:183-90.

137. Bragadottir G, Redfors B, Ricksten SE. Effects of levosimendan on glomerular filtration rate, renal blood flow, and renal oxygenation after cardiac surgery with cardiopulmonary bypass: a randomized placebo-controlled study. Crit Care Med. 2013;41:2328-35.

138. Singh P, Ricksten SE, Bragadottir G, Redfors B, Nordquist L. Renal oxygenation and haemodynamics in acute kidney injury and chronic kidney disease. Clin Exp Pharmacol Physiol. 2013;40:138-47.

139. Lannemyr L, Ricksten S-E, Rundqvist B. Andersson B, Bartfay S-E, Ljungman C, Dahlberg P, Bergh N, Hjalmarsson C, Gilljam T, Bollano E, Karason K., Differential Effects of Levosimendan and Dobutamine on Glomerular Filtration Rate in Patients With Heart Failure and Renal Impairment:A Randomized Double-Blind Controlled TrialJ Am Heart Assoc. 2018;7: e008455. DOI: 10.1161/JAHA.117.008455

140. Fedele F, Bruno N, Brasolin B, Caira C, D'Ambrosi A, Mancone M. Levosimendan improves renal function in acute decompensated heart failure: possible underlying mechanisms. Eur J Heart Fail. 2014;16:281-8.

141. Damman K, Voors AA. Levosimendan improves renal function in acute decompensated heart failure: Cause and clinical application. Editorial to: "Levosimendan improves renal function in patients with acute decompensated heart failure: Comparison with dobutamine by Yilmaz et al." Cardiovasc Drugs Ther. 2007;21:403-4.

142. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure—pathophysiology, evaluation, and therapy. Nat Rev Cardiol. 2015;12:184-92.

143. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E.

Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2016;18:8-27.

144. Santoro F, Ieva R, Ferraretti A, Ienco V, Carpagnano G, Lodispoto M, Di Biase L, Di Biase M, Brunetti ND. Safety and feasibility of levosimendan administration in takotsubo cardiomyopathy: a case series. Cardiovasc Ther. 2013;31:e133-7.

145. Altenberger J, Gustafsson F, Harjola VP, Karason K, Kindgen-Milles D, Kivikko M, Malfatto G, Papp Z, Parissis J, Pollesello P, Pölzl G, Tschöpe C. Levosimendan in Acute and Advanced Heart Failure: An Appraisal of the Clinical Database and Evaluation of Its Therapeutic Applications. J Cardiovasc Pharmacol 2018;71(3):129-136

146. Landoni G, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, Guarracino F, Zangrillo A. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med. 2012;40:634–646

147. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation. 2003;107(1):81-6

148. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T; REVIVE Heart Failure Study Group. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail. 2013;1(2):103-11.

149. Pollesello P, Parissis J, Kivikko M, Harjola VP. Levosimendan meta-analyses: Is there a pattern in the effect on mortality? Int J Cardiol 2016;209:77-83

150. Kivikko M, Pollesello P, Tarvasmäki T, Sarapohja T, Nieminen MS, Harjola VP. Effect of baseline characteristics on mortality in the SURVIVE trial on the effect of levosimendan vs

dobutamine in acute heart failure: Sub-analysis of the Finnish patients. Int J Cardiol 2016;215:26-31

151. Chang W, Xie JF, Xu JY, Yang Y. Effect of levosimendan on mortality in severe sepsis and septic shock: a meta-analysis of randomised trials. BMJ Open 2018;8(3):e019338.

BOX 1: Expected effects of Levosimendan in Intensive Care Unit Settings

- General hemodynamic support
- Increased ejection fraction and cardiac index without increase of oxygen consumption
- Periferal vasodilation and reduction of tissues and organ hypoperfusion
- Increased GFR and renal function
- Decrease in need for cathecolamines
- Sustained effects
- No increase of long-term mortality

BOX 2: Intensive Care Unit Settings in which the use of Levosimendan has been described

- Cardiogenic shock
- Septic shock
- Weaning from ventilator
- Weaning from extracorporeal membrane oxygenation
- Pulmonary hypertension and right ventricular dysfunction
- Need for hemidynamic support in patients with diuretic resistance

BOX 3: recommended dosage of levosimendan when used in Intensive Care Unit Settings

- Levosimendan dosage should be guided by following the blood pressure;
- Bolus should be omitted or used only if SBP is ≥100 mm Hg;
- An infusion rate range of 0.05–0.2 $mg \times kg^{-1} \times min^{-1}$ starting at 0,1 $mg \times kg^{-1} \times min^{-1}$ and up-or down-titrated to the doses which gives hemodynamic stability while avoiding adverse effects such hypotension and/or arrhythmias;
- Hypovolaemia and hypokalemia should be avoided before and during treatment;
- The presence of a long-lived metabolite is associated with the persistence of the hemodynamic effects of levosimendan 7-10 days after a single 24-hour infusion of levosimendan;
- levosimendan is mainly used for its hemodynamic effects, and the longer action of its active metabolite is fully consistent with the pharmacologic effects observed in the beginning of the treatment: no increase in the rate of adverse events (hypotension and/or arrhythmia) is observed after the 24-hour infusion of levosimendan.

Legends

Figure 1. Changes in cardiac power output during infusion of levosimendan (○) and dobutamine (●) in patients with acute myocardial infarction re-vascularized by percutaneous coronary intervention and who developed cardiac shock. Data points are mean ± standard deviation. *p<0.05 (Student's t-test). Data from García-González et al. [69].

Figure 2. Confounder-adjusted long-term survival (levosimendan vs control, p=0.04) in 240 patients weaned from extracorporeal membrane oxygenation. Levosimendan was administered within the first 24 h after initiation of ECMO therapy, at a standard dose of 12.5 mg in 24 h. Data from Distelmaier K et al. [108] .

Figure 3. Differential effects of levosimendan (0.1 µg/kg/min) and dopamine (2 µg/kg/min) on renal blood flow (RBF) and glomerular filtration rate (GFR) in 30 post-cardiac surgery patients. The experimental procedure started 4–6 hours after surgery in the ICU during propofol sedation and mechanical ventilation. Cardiac index (CI) was increased by ≈20% by both drugs. From Bragadottir et al. [137]**.**

Figure 1

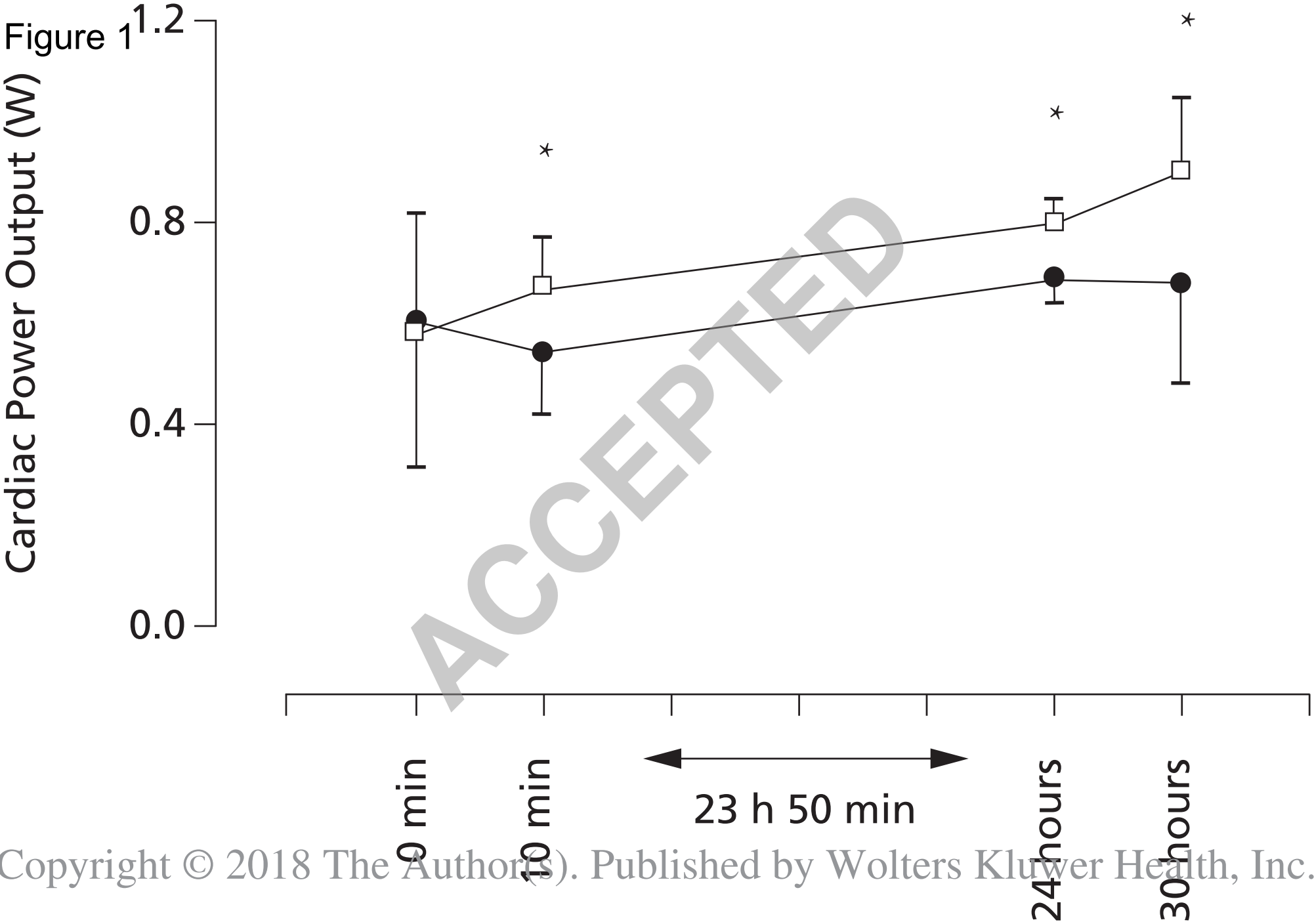

Figure 2

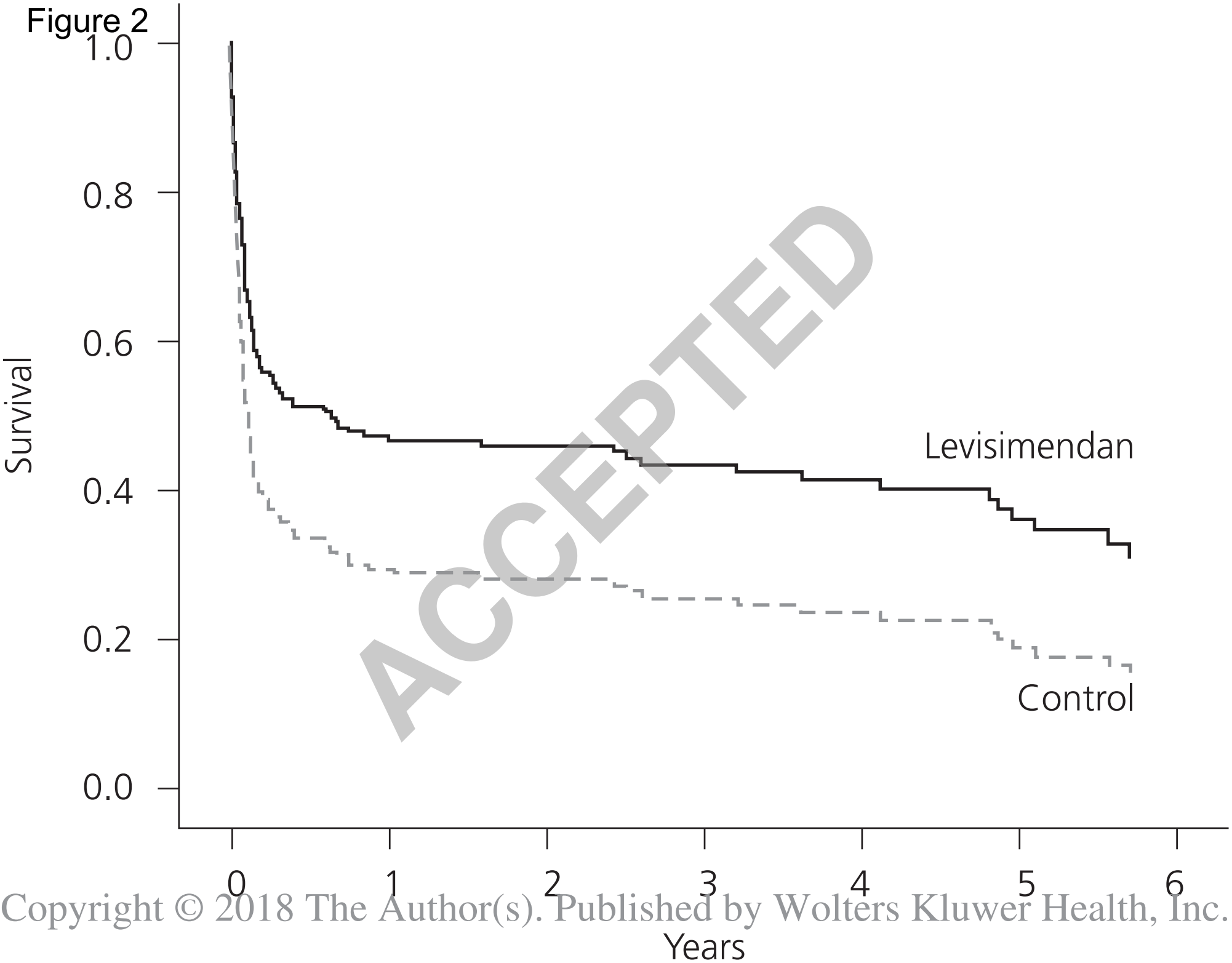

Figure 3